Longitudinal assessment of cardiac involvement in Fabry disease using cardiovascular magnetic resonance imaging

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automatically measured to distinguish TCFA from ThCFA with 99% accuracy. After development using ex vivo VH-OCT data, the AI algorithm was applied in vivo for 13 patients during heart catheterization. The analysis was exempted from institutional review board approval by the Office of the Institutional Review Board at the University of Texas Health Science Center in San Antonio. The sensitivities and specificities for fibrous, calcium, and lipid compared with those provided by the 2 expert readers were 86% and 84%, 80% and 81%, and 82% and 80%, respectively. Example ex vivo and in vivo images are shown, demonstrating the ability to identify accurately fibrous, lipid, and calcium (**Figure 1**).

The traditional classification scheme for IVOCT visualized arterial tissue includes fibrous, lipid, and calcium (4). This study is the first report to automatically classify tissue components with AI based on histological validation and extension into in vivo patient images obtained during heart catheterization. The results suggest that AI based on histological validation can allow identification of clinical morphologies.

Limitations of the present study were misregistration and shallow OCT light penetration depth that limited the potential accuracy of any morphological classifier. To quantify these errors, the pathologists assigned each of the co-registered histology images 1 of 4 morphological categories: fibrocalcific; pathological intimal thickening; ThCFA; and TCFA. The ground truth segmented dataset was likewise classified and then compared with histological classifications. Resulting accuracy of all 4 morphologies was 91%, which suggested an error of 9% from misregistration and shallow penetration depth.

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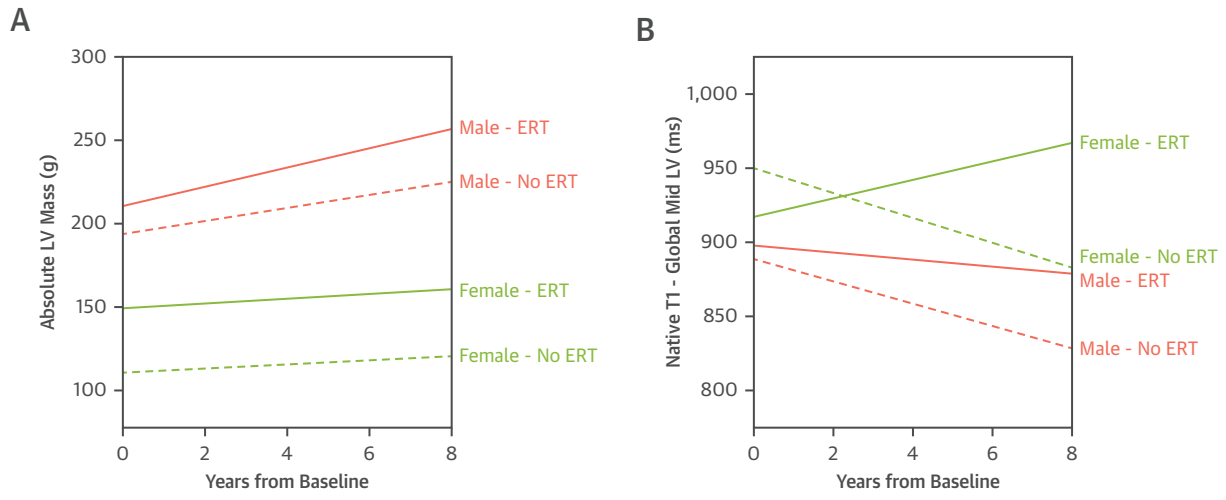
Longitudinal Assessment of Cardiac Involvement in Fabry Disease Using Cardiovascular Magnetic Resonance Imaging

Fabry disease (FD) is an X-linked lysosomal storage disorder resulting in accumulation of sphingolipids in the heart, which leads to progressive left ventricular hypertrophy (LVH), fibrosis, and premature death (1). Although previous studies have tracked changes in mass using echocardiography (2), cardiovascular magnetic resonance (CMR) is the gold standard for reproducible measurement of mass and offers insight into the relationship between sphingolipid deposition, LVH, and fibrosis in FD over time, using T1 and T2 mapping, as well as late gadolinium enhancement (LGE). (3) The aim of this study was to define LV changes in FD over time and to consider use of enzyme replacement therapy (ERT).

This was a multicenter longitudinal study using CMR in 100 patients with FD (gene positive; 44% men; mean age 44 ± 14 years). Local clinical governance and ethical approval was obtained (NRES London 14/LO/1948, UHB clinical governance: RRK6621). Participants underwent 1.5-T CMR (Avanto, Siemens Healthcare, Erlangen, Germany) using a standard protocol that quantified LV mass and tissue characterization with T1 [Modified Look-Locker Inversion recovery sequence, 3(3)3(3)5 sampling scheme] and T2 mapping pre-contrast and inversion recovery imaging for LGE post-contrast. T1 maps were

FIGURE 1 **Change in Absolute LV Mass and Native T1 Over Time, Split by Sex and ERT Status**



(A) Change in left ventricular (LV) mass. Gradient per year: men: no enzyme replacement therapy (ERT) +1.9% versus ERT +2.5%; women: no ERT +1.1% versus ERT +0.9%; $p < 0.05$. No significant differences comparing no ERT versus ERT. **(B)** Change in T1 time. Gradient per year: men: no ERT −7.6 ms vs. ERT −2.4 ms; women: no ERT −8.3 ms vs. ERT +6.2 ms; $p < 0.05$. A significant difference was present comparing no ERT versus ERT in women only ($p < 0.001$).

analyzed using semi-automated segmentation at the mid-LV cavity, with a 20:20 percentage offset and an average of all segments taken (following artefactual segment exclusion), which gave global T1 mapping. LGE was quantified using a threshold of 6 SDs above the mean signal intensity of the reference myocardium.

The median duration of follow-up was 37 months (interquartile range [IQR]: 20 to 60 months), with a median of 2 follow-up visits per patient (range 2 to 6). Fifty percent of patients were on ERT at baseline (37 on agalsidase-alpha and 13 on agalsidase-beta). At baseline, men had higher indexed LV mass (LVMi) and maximum wall thickness (MWT) compared with women (median LVMi: 111.8 g/m^2 [IQR: 85.4 to 149.2 g/m^2] vs. 62.7 g/m^2 [IQR: 56.7 to 82.5 g/m^2]; MWT: 16 mm [IQR: 12 to 18 mm] vs. 10 mm [IQR: 9 to 12 mm]; $p < 0.001$ for both). Thirty-one patients (33%) had LGE at baseline (men: 49% vs. women: 21%; $p = 0.008$), with a similar mass of LGE seen (men 8.5 g [IQR: 3.2 to 19.6 g] vs. women: 7.4 g [IQR: 1.4 to 15.2 g]; $p = 0.359$).

There was an increase in absolute LVM over time ($n = 100$), with a gradient of 2.4% (95% confidence interval [CI]: 1.8% to 3.1%) per year in men ($p < 0.001$) and 1.0% (95% CI: 0.3 to 1.7%) per year in women ($p = 0.005$). Native T1 decreased over time in men (−3.4 ms per year; 95% CI: −6.4 to −0.4; $p = 0.029$), but no significant change was observed in women ($p = 0.831$). Mass of LGE increased by 36.6% (95% CI: 14.0% to 63.7%) per year in men ($p < 0.001$) and by 12.0% (95% CI: 2.0% to 23.0%) per year in women ($p = 0.011$). There were no changes in the proportions of male and female patients with chronic kidney disease, ischemic heart disease, or hypertension over the study period.

Five patients received ERT during follow-up and were excluded from subgroup analysis by ERT status (Figure 1). ERT usage differed by sex, with 32 of 41 (78%) men on ERT compared with 18 of 54 (33%) women ($p < 0.001$). The increase in LVM over time remained significant despite the use of ERT in both men (ERT: 2.5% per year; 95% CI: 1.9% to 3.0%; $p < 0.001$; no ERT: 1.9% per year; 95% CI: 0.3% to 3.6%; $p = 0.020$) and women (ERT: 0.9% per year; 95% CI: 0.1% to 1.8%; $p = 0.025$; no ERT: 1.1% per year; 95% CI: 0.3% to 1.9%; $p = 0.005$). T1 decreased over time in men not on ERT (−7.6 ms per year; 95% CI: −12.6 to −2.5; $p = 0.003$), although there was a tendency to a smaller reduction on ERT (−2.4 ms; 95% CI: −4.6 to −0.1; $p = 0.039$; between groups: $p = 0.064$). However, in women, T1 decreased over time in those not on ERT (−8.3 ms per year; 95% CI: −12.6 to −3.9; $p < 0.001$) but increased in the ERT group (+6.2 ms per year; 95% CI: 2.0 to 10.4; $p = 0.004$; between groups: $p < 0.001$).

This longitudinal CMR study was consistent with a sex-specific myocardial response in FD. Men had more advanced cardiac involvement at baseline and progressed at a greater rate than women, despite use

of disease-modifying therapy. During this study, these changes were less clear in women, and the impact of ERT was more pronounced. Although LV mass increased in women on ERT, T1 time increased, which could be consistent with either a sex-dependent response to therapy or a difference in myocardial response to storage. Limitations included the small sample size and lack of established prognostic T1 data, which made the relevance and importance of this parameter in disease progression unclear.

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Regional Left Ventricular Myocardial Work Indices and Response to Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is a well-established heart failure (HF) treatment and exerts its effects through restoration of synchronous ventricular contraction. Myocardial work (MW) is a novel semiautomatic echocardiographic method which characterizes the efficacy of the left ventricular (LV) contraction by evaluating the amount of energy loss (wasted work [WW]) and the amount of work performed (constructive work [CW]) for each myocardial segment (1). We investigated regional differences in CW and WW between the septum and the lateral wall, its potential implications for CRT response, as well as the pattern of changes occurring early after CRT implantation. The review board of the Leiden University Medical Center approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

A total of 168 patients (71% men, mean age 65 ± 10 years) with HF and sinus rhythm were included. Speckle-tracking echocardiography was used to assess MW at baseline and early after CRT implantation (within the first 5 days). LV global longitudinal strain, noninvasive blood pressure measurements, and valves opening and closure times were integrated to construct pressure-strain loops. CW and WW of the septal and lateral walls were calculated as the average values of basal and mid-ventricular segments. CRT response was defined as a decrease in LV end-systolic volume ≥15 % at 6-month follow-up. The interobserver and intraobserver variability of MW indices was assessed calculating the intraclass correlation coefficient (ICC) on 35 randomly selected patients. Both interobserver and intraobserver variability was excellent for segmental CW (ICC >0.93) and acceptable for segmental WW (ICC >0.75).

Table 1 summarizes baseline characteristics and regional MW indices before and after CRT implantation in the overall population, CRT responders, and nonresponders. Nonischemic etiology of HF was significantly more frequent in CRT responders ($p = 0.027$). At baseline, CRT responders demonstrated significantly larger septal WW ($p = 0.038$) and lateral CW ($p = 0.005$) compared with nonresponders.